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# Does high-dose opioid anesthesia exacerbate ischemic spinal cord injury in rabbits?

Yumiko Shirasawa, Mishiya Matsumoto, Manabu Yoshimura, Atsuo Yamashita, Shiro Fukuda, Kazuyoshi Ishida, and Takefumi Sakabe

Department of Anesthesiology, Yamaguchi University Graduate School of Medicine, 1-1-1 Minami-Kogushi, Ube 755-8505, Japan

**Abstract**

*Purpose.* Intrathecal morphine given during a post-ischemic period has been reported to have the potential to exacerbate ischemic spinal cord injury. However, it remains unknown whether synthetic opioids administered systemically exacerbate ischemic injury. We sought to compare the damage of the spinal cord after transient spinal cord ischemia in rabbits anesthetized with three different regimens; isoflurane, fentanyl with isoflurane, and remifentanil with isoflurane.

*Methods.* We assigned rabbits to three groups ($n$ = 9 in each); an isoflurane group (isoflurane 1 minimum alveolar concentration [MAC]), a fentanyl group (isoflurane 0.5 MAC + 100 $\mu g \cdot kg^{-1}$ IV fentanyl given over 30 min before aortic occlusion), and a remifentanil group (isoflurane 0.5 MAC + 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ IV remifentanil started 30 min before aortic occlusion and maintained until 1 h after reperfusion). Spinal cord ischemia was produced by occluding the abdominal aorta for 13 min. Hindlimb motor function (score range: 4, normal to 0, paraplegia) was assessed daily for 7 days, and then the number of normal neurons in the anterior spinal cord was counted.

*Results.* Severe motor dysfunction (score ≤ 1) was observed in seven, four, and five animals in the isoflurane, fentanyl, and remifentanil groups, respectively. There were no significant intergroup differences in neurological scores. There were no differences in the numbers of normal neurons among the three groups (22 ± 22, 42 ± 30, 33 ± 28, respectively).

*Conclusion.* Our results suggest that neither IV fentanyl nor IV remifentanil added to 0.5 MAC isoflurane exacerbated ischemic spinal cord injury in rabbits when compared to 1 MAC isoflurane.

**Key words** Spinal cord ischemia · Opioid · Fentanyl · Remifentanil · Rabbit

*Address correspondence to*: M. Matsumoto
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## Introduction

Preventing ischemic injury of the spinal cord during thoracoabdominal aortic surgery is a challenging issue. However, no single strategy has yet been proven effective in the clinical setting. Therefore, it is of great importance at present not to use drugs that may have adverse effects on the ischemic spinal cord. Opioids have been widely used as anesthesia/analgesia regimens for thoracoabdominal aortic surgery. However, it has been reported, by Kakinohana et al. [1], that epidural morphine (4 mg), given for pain relief in a patient who underwent repair of a thoracoabdominal aortic aneurysm, triggered lower-extremity paraparesis, and that the paraparesis was reversed by naloxone. These authors then showed that, in rats, large intrathecal (IT) doses of morphine given during a post-ischemic period induced spastic paraparesis after a noninjurious interval (6 min) of spinal cord ischemia [1]. In addition, a series of experiments using the same ischemia model demonstrated that mu and delta, but not kappa, opioid agonists given intrathecally could induce spastic paraparesis [2]. It was suggested that opioids administered intrathecally during or shortly after transient aortic occlusion may be associated with a potential risk of paraparesis and the corresponding development of neurological dysfunction [3]. Furthermore, based on the reported beneficial effects of naloxone, both in animal models of spinal cord ischemia [4] and in patients undergoing thoracoabdominal aortic replacement [5], naloxone has been used during thoracoabdominal aortic surgery at some institutes. Nevertheless, it has not been determined whether clinically relevant regimens of synthetic opioids, i.e., intravenous (IV) fentanyl or remifentanil, added to a low concentration of inhalational anesthetic exacerbate ischemic spinal cord injury.

The aim of the present study was to compare the damage of the spinal cord after transient spinal cord ischemia in rabbits anesthetized with three different

regimens; isoflurane, fentanyl with isoflurane, and remifentanil with isoflurane. We used a well-characterized rabbit model of spinal cord ischemia.

## Materials and methods

The study protocol was approved by the Ethics Committee for Animal Experiments at Yamaguchi University Graduate School of Medicine. Twenty-seven fasted male New Zealand white rabbits weighing 2.3 ± 0.2 kg (mean ± SD) were used in this study.

After an overnight fast with unrestricted access to water, rabbits were anesthetized in a plastic box with 3% isoflurane in oxygen. A catheter was inserted in an ear vein for the administration of fluid (lactated Ringer's solution 10 $ml \cdot kg^{-1} \cdot h^{-1}$) and drugs, and pentobarbital (30 mg) was administered to facilitate tracheal intubation. After the placing of a 3-mm cuffed endotracheal tube, the inspired gas mixture was changed to isoflurane 2%-3% in 40% oxygen/60% nitrogen, and the rabbits' lungs were mechanically ventilated. Temperatures were monitored with a calibrated esophageal thermistor (model MG-type 209; Nihon Koden, Tokyo, Japan) and a needle-type thermistor (model PTC-201; Unique Medical, Tokyo, Japan) inserted into the paravertebral muscle at the L4–5 level. The paravertebral muscle temperature was controlled throughout the study at approximately 38.0°C with a heating lamp and warming pad. PE-60 catheters were inserted into both femoral arteries to measure blood pressure proximal and distal to the level of the aortic occlusion. The right-side catheter was advanced 5 cm into the abdominal aorta, the left one was advanced 18 cm.

Spinal cord ischemia was produced as previously reported [6,7]. In brief, with the animal in the right lateral decubitus position, the abdominal aorta was exposed retroperitoneally at the level of the left renal artery. A PE-60 catheter was placed around the aorta immediately distal to the left renal artery for later occlusion of the aorta. Then, an occluder tube (16-F rubber tube) was tunneled to the skin.

After the completion of surgery, the animals were randomly assigned to one of the following groups ($n$ = 9 in each): an isoflurane group, a fentanyl group, or a remifentanil group. In the isoflurane group, end-tidal isoflurane concentration was maintained at 2% (1 minimum alveolar concentration [MAC] for the New Zealand white rabbit [8]), and saline (solvent) was infused through the catheter inserted in an ear vein. In the fentanyl group, end-tidal isoflurane concentration was decreased to 1% (0.5 MAC) and fentanyl solution (total amount of 100 $\mu g \cdot kg^{-1}$, 20 $\mu g \cdot ml^{-1}$) was administered intravenously over 30 min just before aortic occlusion. In the remifentanil group, end-tidal isoflurane concentration was decreased to 1% (0.5 MAC) and remifentanil solution (1 $\mu g \cdot kg^{-1} \cdot min^{-1}$, 10 $\mu g \cdot ml^{-1}$) was administered intravenously from 30 min before aortic occlusion until 1 h after reperfusion. The fentanyl and remifentanil solutions were prepared by the dilution of fentanyl citrate solution (Daiichi Sankyo, Tokyo, Japan) and remifentanil hydrochloride (Janssen Pharmaceutical, Tokyo, Japan), respectively, with saline. When the proximal mean arterial blood pressure was lower than 60 mmHg, phenylephrine was infused to maintain blood pressure.

Spinal cord ischemia was produced by occluding the abdominal aorta for 13 min [6,7]. Segmental spinal cord evoked potentials (SSCEPs) were recorded every 1 min for 7 min after aortic occlusion and for 15 min following reperfusion, stimulating the left sciatic nerve and recording in a bipolar fashion (L5 and L6). We measured the amplitude of the third negative wave (N3) that represents the postsynaptic component [9]. After the final recording of SSCEPs, wounds were closed and anesthesia was discontinued. Diazepam (0.2 $mg \cdot kg^{-1}$, intramuscular [IM]) was given to reduce surgical stress. To alleviate postsurgical pain, pentazocine hydrochloride (1 $mg \cdot kg^{-1}$, IM) was given in the isoflurane and remifentanil groups, but not in the fentanyl group, because an analgesic effect of fentanyl appeared to remain.

The animals were neurologically assessed at 12 h and then daily for 7 days after reperfusion by an observer unaware of the treatment group, using the 5-point score system proposed by Drummond and Moore [10]: 4, normal motor function; 3, ability to draw legs under body and hop, but not normally; 2, some lower-extremity function with good antigravity strength, but inability to draw legs under body and/or hop; 1, poor lower-extremity function, but weak antigravity movement only; 0, paraplegic with no lower-extremity function.

After the final neurological assessment (7 days after reperfusion), histopathologic examination was performed [6,7]. Normal neurons in the anterior spinal cord at the level of L5 (anterior to a line drawn through the central canal perpendicular to the vertical axis) were counted in two sections, stained with hematoxylin and eosin, for each animal and averaged. Normal neurons were identified by the presence of Nissl substances and the absence of cytoplasmic eosinophilia or pyknotic homogeneous nuclei, as reported previously [9].

Parametric data values are presented as means ± SD. Physiological variables were analyzed by repeated-measures analysis of variance followed by factorial analysis of variance. Where differences were identified, Scheffé's post-hoc test for intergroup comparisons was performed. The time for the N3 wave of SSCEPs to disappear after aortic occlusion or to appear after reperfusion, and the anesthetic time, were analyzed by facto-

**Table 1.** Physiological variables

| | MAP proximal (mmHg) | MAP distal (mmHg) | HR (bpm) | Temp esoph (°C) | Temp paravert (°C) | pH | $Pa_{O_2}$ (mmHg) | $Pa_{CO_2}$ (mmHg) | Glucose ($mg \cdot dl^{-1}$) | Hct (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| Isoflurane group | | | | | | | | | | |
| Pre-ischemia | 70 ± 8 | 59 ± 5 | 278 ± 41 | 38.0 ± 0.4 | 37.9 ± 0.1 | 7.37 ± 0.03 | 194 ± 12 | 40 ± 2 | 177 ± 22 | 33 ± 4 |
| Ischemia 5 min | 66 ± 6 | 9 ± 1 | 274 ± 38 | 37.9 ± 0.2 | 37.9 ± 0.1 | | | | | |
| Reperfusion 15 min | 75 ± 8 | 63 ± 5 | 254 ± 19 | 37.9 ± 0.1 | 37.9 ± 0.1 | 7.36 ± 0.03 | 177 ± 26 | 39 ± 2 | 180 ± 31 | 33 ± 2 |
| Fentanyl group | | | | | | | | | | |
| Pre-ischemia | 81 ± 9* | 70 ± 9* | 197 ± 22* | 38.1 ± 0.3 | 37.6 ± 0.3 | 7.34 ± 0.03 | 202 ± 27 | 40 ± 2 | 167 ± 40 | 33 ± 2 |
| Ischemia 5 min | 74 ± 14 | 9 ± 2 | 191 ± 28* | 38.0 ± 0.2 | 37.5 ± 0.3 | | | | | |
| Reperfusion 15 min | 74 ± 8 | 62 ± 7 | 206 ± 27* | 37.9 ± 0.1 | 37.5 ± 0.3 | 7.33 ± 0.03 | 197 ± 26 | 39 ± 3 | 155 ± 28 | 32 ± 2 |
| Remifentanil group | | | | | | | | | | |
| Pre-ischemia | 73 ± 6 | 66 ± 6 | 214 ± 39* | 38.3 ± 0.2 | 37.9 ± 0.3 | 7.37 ± 0.04 | 202 ± 13 | 40 ± 3 | 174 ± 43 | 35 ± 2 |
| Ischemia 5 min | 74 ± 7 | 9 ± 2 | 205 ± 21* | 38.2 ± 0.2 | 37.9 ± 0.3 | | | | | |
| Reperfusion 15 min | 79 ± 8 | 67 ± 7 | 187 ± 27* | 38.0 ± 0.2 | 37.9 ± 0.2 | 7.36 ± 0.04 | 199 ± 9 | 40 ± 3 | 191 ± 59 | 33 ± 2 |

* $P < 0.05$ vs isoflurane group
Data values are means ± SD
MAP, mean arterial pressure; HR, heart rate; Temp, temperature; esoph, esophageal; paravert, paravertebral; Hct, hematocrit

rial analysis of variance. Hindlimb motor function and the number of normal neurons in the anterior spinal cord were analyzed with nonparametric methods (Kruskal-Wallis test or Mann-Whitney *U*-test). $P < 0.05$ was considered statistically significant.

## Results

All animals survived until the final neurological assessment. There were no significant differences in the physiological variables among the three groups, except for pre-ischemic blood pressure and heart rate during the peri-ischemic period (Table 1).

In all groups, the time required for the N3 wave of SSCEPs to disappear was 4 to 7 min, whereas the times required for the N3 wave to appear after reperfusion were 9.6 ± 2.7, 7.9 ± 2.1, and 8.0 ± 3.5 min in the isoflurane, fentanyl, and remifentanil groups, respectively. Anesthetic times were 222 ± 38, 212 ± 29, and 210 ± 11 min in the isoflurane, fentanyl, and remifentanil groups, respectively. There were no significant differences in the times required for the N3 wave to disappear and to appear, nor were there any significant differences in anesthetic times among the three groups.

Severe motor dysfunction (score ≤ 1) was observed in seven, four, and five of nine animals in the isoflurane, fentanyl, and remifentanil groups, respectively (Fig. 1). There were no significant differences in motor function scores among the three groups at any time point. In the animals with severe motor dysfunction, irrespective of the treatment, few normal neurons were seen in the anterior spinal cord, and destruction of the entire gray matter was observed, with inflammatory changes (Fig. 2). In the animals with normal motor function (score 4), the structure of the gray and white matter of the spinal cord was well maintained and motor neurons preserved an almost normal appearance. There were no significant differences in the numbers of morphologically normal-appearing neurons 7 days after reperfusion among the three groups (Fig. 3). The neurological and histopathologic outcomes in the isoflurane group in the present study appeared to be almost the same as those in the control group (2% isoflurane) in our previous study [7].

## Discussion

Since Kakinohana et al. [1] reported the occurrence of paraparesis with epidural morphine in a patient who underwent thoracoabdominal aortic repair, together with their report of paraparesis with IT morphine in rats subjected to a noninjurious interval of spinal cord ischemia, it has been a great concern for clinicians whether

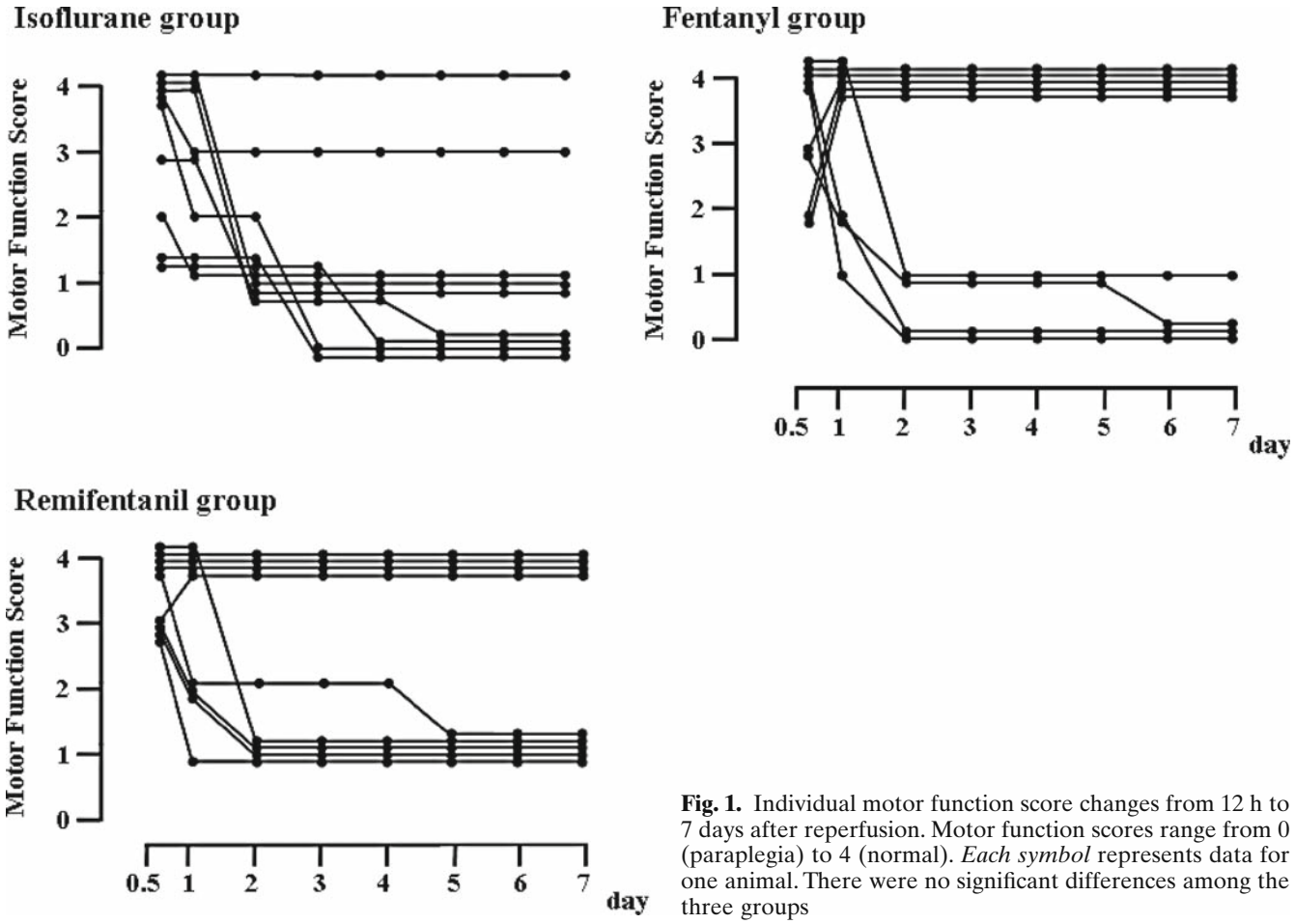


**Fig. 1.** Individual motor function score changes from 12 h to 7 days after reperfusion. Motor function scores range from 0 (paraplegia) to 4 (normal). *Each symbol* represents data for one animal. There were no significant differences among the three groups

systemically administered synthetic opioids induce or exacerbate damage in the spinal cord subjected to transient ischemia. However, no reported data have been available. Thus, we compared the effects of three different anesthetic regimens frequently used in the clinical setting; isoflurane (1 MAC) and fentanyl or remifentanil added to a low concentration of isoflurane (0.5 MAC).

It is known that a long duration of ischemia (>20 to 25 min) causes acute-onset paraplegia, whereas an intermediate duration (13–5 min) causes delayed-onset motor dysfunction in most animals [7,11]. Thus, we chose 13-min ischemia, which would be an appropriate duration of the insult to determine whether the test treatments either alleviated or exacerbated damage.

In the present study, we demonstrated that the rabbits anesthetized with 100 $\mu g \cdot kg^{-1}$ of IV fentanyl with 0.5 MAC isoflurane or 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of IV remifentanil with 0.5 MAC isoflurane exhibited neurological and histopathologic outcomes after 13 min of ischemia comparable to those in the rabbits anesthetized with 1 MAC isoflurane. It has been reported that the effective analgesic dose ranges of fentanyl [12] and remifentanil [13] in rabbits are similar to those in humans. However, in the present study, we chose higher doses of fentanyl and remifentanil (twice as high as the near-maximal doses) to see if they exerted any adverse effects. We found that no adverse effects were shown on neurological or histopathologic outcomes. Although the possibility that much higher doses of fentanyl or remifentanil may exacerbate ischemic spinal cord injury remains undetermined, we think it unlikely that the clinically relevant IV regimens of fentanyl and remifentanil added to a low concentration of isoflurane exacerbated the ischemic spinal cord injury in rabbits.

With regard to the effects of intravenously administered opioids on neuronal injury in other models, there have been a few reports. In the rat forebrain ischemia model, controversial results were reported with preischemic IV fentanyl. Morimoto et al. [14] reported that fentanyl (400 $\mu g \cdot kg^{-1}$ followed by an infusion of 16 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 20 min) did not adversely affect neurological or histopathologic outcomes 4 days after reperfusion. In contrast, Kofke et al. [15] reported that fentanyl (50 $\mu g \cdot kg^{-1}$ followed by an infusion of 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$, or 800 $\mu g \cdot kg^{-1}$ followed by an infusion of 32 $\mu g \cdot kg^{-1} \cdot min^{-1}$

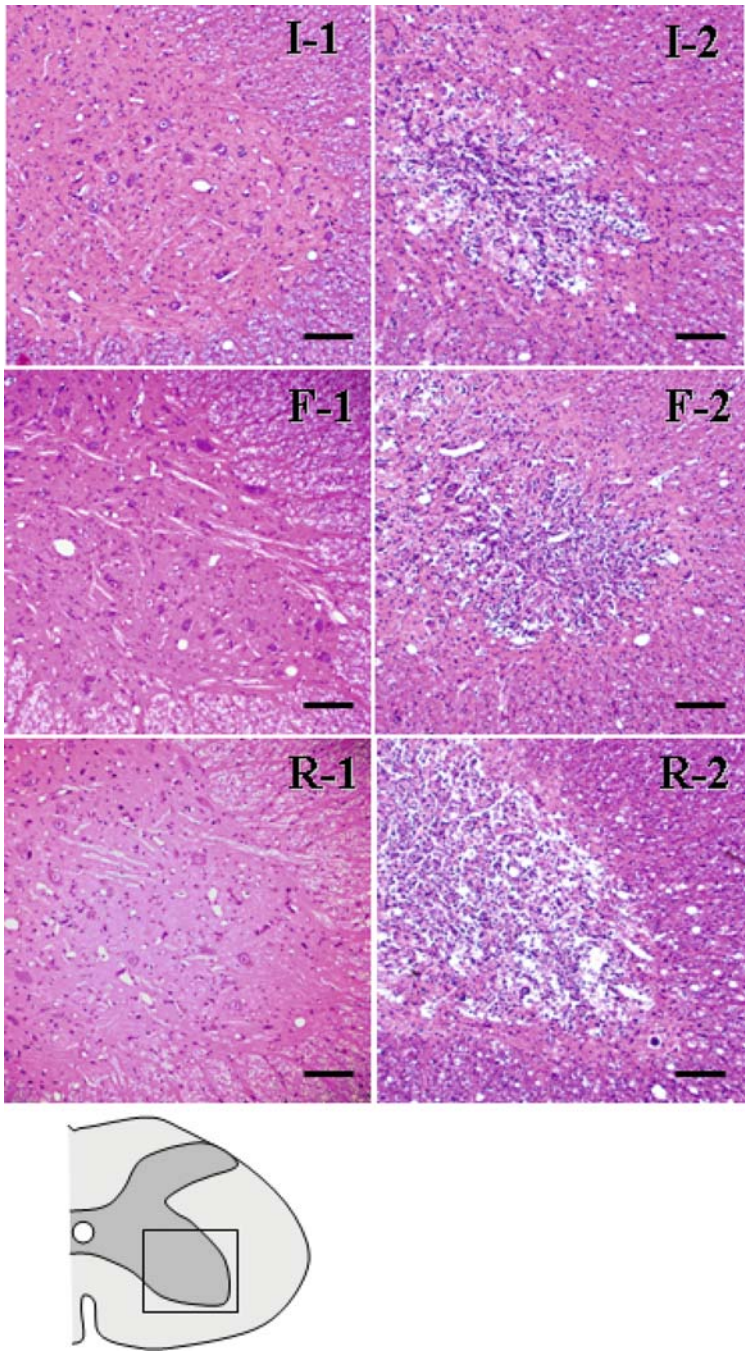


**Fig. 2.** Light microphotographs of the spinal cord (L5 level,). *I-1* and *I-2*, the isoflurane group; motor function scores 4 and 0, respectively. *F-1* and *F-2*, the fentanyl group; motor function scores 4 and 0, respectively. *R-1* and *R-2*, the remifentanil group; motor function scores 4 and 1, respectively. In I-1, F-1, and R-1, the structure of the gray matter of the spinal cord was well maintained and motor neurons preserved an almost normal appearance. In I-2, F-2, and R-2, few normal neurons were seen in the anterior spinal cord, and destruction of the entire gray matter was observed, with inflammatory changes. H & E, ×100; *bars*, 200 μm

for 30 min) exacerbated histopathology 18 h after reperfusion. The dose used in the study of Morimoto et al. [14], which was lower than the higher dose used in the study of Kofke et al. [15], was sufficient to cause a seizure pattern on electroencephalography that may have resulted in a hypermetabolic state. Nonetheless, fentanyl did not worsen the outcome. In a rat compressive spinal cord injury model, Cole et al. [16] reported that the neurological outcome with fentanyl (57 $\mu g \cdot kg^{-1}$ subcutaneously)/$N_2O$ (65%) anesthesia was improved compared with that in the awake state. These authors suggested that fentanyl/$N_2O$ anesthesia did not produce an adverse effect on neurological outcome following a compressive spinal cord injury; in fact, the outcome was even better than that in the awake state [16]. The concomitant IT injection of naloxone did not further improve (or worsen) the neurological outcome [16]. These results do not support the supposition that IV opioid anesthesia produces an adverse effect upon neurological outcome following a compressive spinal cord injury. Our results are in accordance with those reported by Cole et al. [16], despite the different spinal cord injury models used.

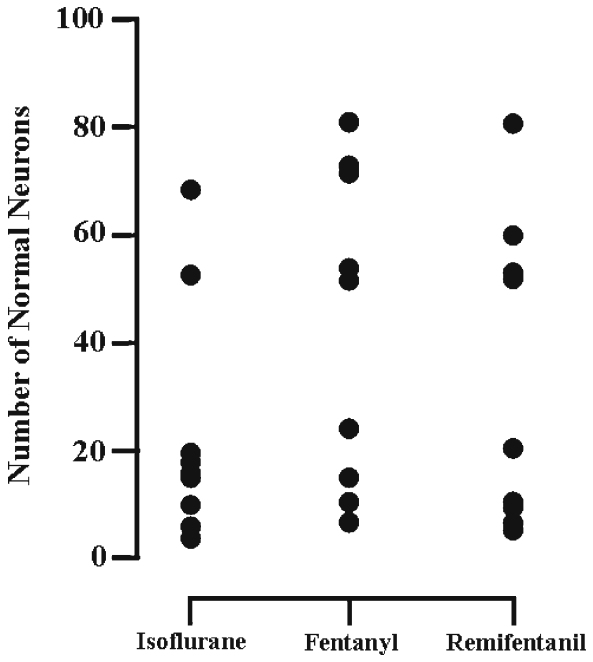


**Fig. 3.** The number of normal neurons in the anterior spinal cord (L5 level) 7 days after reperfusion. *Each symbol* represents data for one animal. There were no significant differences among the three groups

There are some limitations of the present study. First, isoflurane, though used at a low concentration (0.5 MAC), may attenuate the effects of fentanyl and remifentanil. However, it is not justified to subject animals to ischemic injury without sedation. Because the neurological outcome in the 1 MAC isoflurane group, though statistically insignificant, appeared poorer than that in the fentanyl and remifentanil groups, it is unlikely that 0.5 MAC isoflurane would have masked the adverse effect of fentanyl and remifentanil. Second, the postischemic analgesia regimens were not the same in our three groups. We gave pentazocine to the animals in the isoflurane and remifentanil groups after discontinuation of the drugs, but no analgesic was given to the fentanyl group, because an analgesic effect of fentanyl appeared to remain. Although the possibility cannot be completely excluded that the difference in the analgesic regimens for postsurgical care affected the results, we believe that this is unlikely, because pentazocine is known not to exacerbate ischemic spinal cord injury [2]. Third, there may have been a type-II error in the present study because of the limited number of animals in each group. However, there seemed to be no tendency that the neurological and histopathologic outcomes in the fentanyl and remifentanil groups were worse than those in the isoflurane group; indeed, the opposite was the case. Fourth, because the severity of the insult tested was limited to one episode (13 min of ischemia), the effects of opioids on ischemic spinal cord injury with insults of different severity were not shown.

In summary, neither 100 $\mu g \cdot kg^{-1}$ of IV fentanyl nor 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of IV remifentanil added to a low concentration of isoflurane (0.5 MAC) exacerbated ischemic injury in rabbits when compared to 1 MAC isoflurane. Because it has been reported that the effective analgesic dose ranges of fentanyl and remifentanil in rabbits are similar to those in humans, it seems unlikely that clinically relevant doses of IV fentanyl or IV remifentanil exacerbate ischemic spinal cord injury.

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